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(54) Title: SEBUM-DISSOLVING NONAQUEOUS MINOXIDIL FORMULATION

(57) Abstract

Novel topical formulations of minoxidil comprising minoxidil; a solvent for minoxidil; a non-polar solvent which renders the formulation approximately the same polarity as human sebum; and a cosolvent which enhances the delivery of minoxidil through the stratum corneum.

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# SEBUM-DISSOLVING NONAQUEOUS MINOXIDIL FORMULATION

## DESCRIPTION

The present application provides a novel composition of matter. More particularly, the present application provides a new formulation for known pharmaceutical products. Most particularly, the present application provides a topical composition containing minoxidil which dissolves sebum, the oil surrounding the hair follicle, and provides a means for penetrating the outer skin layer, the stratum corneum.

Minoxidil is a well-known pharmaceutical compound. It is marketed by The Upjohn Company as the active ingredient in LONITEN® Tablets for the treatment of hypertension. It is also useful in topical compositions for the treatment of baldness. The structure and use of this compound for this purpose is described in U.S. Patents 4,139,619 and 4,596,812. This compound has varying degrees of efficacy for hair growth purposes, depending on the patient, the degree of baldness, the dose, and the nature of the topical composition. Currently, topical minoxidil is administered in a composition containing propylene glycol, ethanol and water.

## INFORMATION DISCLOSURE

U.S. Patent 4,139,619 discloses topical minoxidil compositions containing carriers selected from ointments, lotions, pastes, jellies, sprays, and aerosols. U.S. patent 4,596,812 also discloses topical compositions of minoxidil. Cooper, J. Pharm. Sci. 73:1153 (1984) describes means for increasing skin transport of certain pharmaceutical compounds.

## SUMMARY OF THE INVENTION

The present invention particularly provides:

(1) A topical hair growth composition comprising:

(a) minoxidil;

(b) a solvent capable of dissolving minoxidil;

(c) a non-polar solvent which renders the formulation approximately the same polarity as human sebum; and

(d) a cosolvent having a polarity between that of the solvent capable of dissolving minoxidil and the non-polar solvent, which enhances the delivery of minoxidil through the stratum corneum, said cosolvent in an amount less than that which causes skin irritation.

The present invention thus provides a non-aqueous topical

minoxidil formulations having improved efficacy.

By minoxidil is meant the 2,4-pyrimidinediamine, 6-(1-piperidinyl)-3-oxide, analogs as well as salts thereof, as described in U.S. Patents 4,139,619, and 4,596,812, which patents are expressly incorporated by reference herein.

Suitable solvents for minoxidil include propylene glycol, 1,3-butylene diol, polyethylene glycol 200 (PEG 200), polyethylene glycol 400 (PEG 400), isopropanol, ethanol, methanol, 1,5 pentane diol, 1,2,6-trihydroxyhexane, 1,7-heptanediol, 1,4 butane diol and N-methylpyrrolidone and related compounds (see, e.g., J. Pharm. Pharmacol. 37:298-304 (1985).

Suitable non-polar solvents include silicone oils such as the following volatile silicone oils: Dow Corning - 344 fluid; Dow Corning - 345 fluid; Union Carbide - V.S. 7207; Union Carbide - V.S. 7158; and Union Carbide - V.S. 7349, and the following nonvolatile (or less volatile) silicone oils: Dow Corning - 200 fluids of various viscosities; and Union Carbide - L-45 fluids of various viscosities.

Suitable cosolvent/penetration enhancers include alcohols such as butanol, hexanol, octanol, decanol, dodecanol and oleyl alcohol; amines, such as isopropyl amine, diisopropyl amine, triethyl amine, triethanol amine and ethylene diamine; carboxylic acids, such as oleic acid, linoleic acid and linolenic acid; esters, such as dibutyl sebacate, dibutyl phthalate, butyl benzoate and ethyl caprate; and others, such as AZONE®, N methyl pyrolidone, bile salts and urea. Oleyl alcohol is the preferred cosolvent.

To aid in the miscibility of the components, preferably an additional cosolvent is added to the cosolvent having a polarity between the minoxidil solvent and the non-polar solvent oleyl alcohol. Thus, for oleyl alcohol, the preferred penetration-enhancer and cosolvent, isopropanol is the preferred additional cosolvent making a miscible solution with volatile silicones (e.g. Dow Corning 344 fluid). The isopropanol is used in the range of from 16 to 27% and makes single phase solutions of all mixtures of interest. The volatility of the isopropanol reduces some of the oiliness caused by the oleyl alcoh l, since lesser amounts f oleyl alcoh l need be used in these formulati ns to make a miscible soluti n than were used prior to the addition of isopropan l. Ethanol can als be used as a

less chemically "smelling" cosolvent f r these vehicles, but ethanol must be present at concentrations 5-10% greater than isopr panol and the resulting vehicle is not as effective in solubilizing sebum.

Sebum is the relatively non-polar material excreted from the sebaceous glands located in the hair follicle. In order to stimulate hair growth, it is desirable to target topical minoxidil formulations to the sebaceous glands. The present composition, which is miscible with human sebum, accomplishes this purpose.

Hildebrand solubility coefficients (HSC) (see Vaughn, J. Soc. Cosmet. Chem. 36:319-333 (Sept/Oct 1985)) are used to characterize a miscible vehicle using a sebum solubilizing agent of low (i.e. non-polar) Hildebrand solubility coefficient in combination with a skin penetration aid with a Hildebrand solubility coefficient intermediate between that of the non-polar sebum solvent and the more polar minoxidil solvent. The resulting vehicle has Hildebrand solubility coefficient close to that of human sebum and can completely solubilize the amount of sebum on the scalp. The currently used more polar vehicles for minoxidil cannot solubilize this amount of sebum.

Based upon the composition of synthetic (or artificial) sebum, the Hildebrand (HSC) solubility coefficient for sebum is about 7 or 8 cal $^{1}/_{2}$ cm $^{-3/2}$. Minoxidil shows its best solubility in propylene glycol which has an HSC of 14. Miscibility (the ability of two or more liquids to mix in all proportions) is shown on this scale typically when there is a difference of 2 units. Therefore, in order to lower the HSC of the vehicle from that of pure propylene glycol down to 2 of sebum, a solvent with HSC below that of sebum must be chosen. One of the most suitable solvents is volatile silicone oil with a HSC of about 5.8-5.9 Since the silicone oils are totally immiscible with the propylene glycol, it is necessary to add a cosolvent to render the two more miscible.

This cosolvent could have only HSC between 6 and 14, however, the midpoint (about 10) should require the smallest amount of cosolvent and is thus preferred.

Minoxidil is not well absorbed through the skin in the prior art formulations (e.g., propylene glycol/ethanol/water). Thus, addition of a vehicle component that enhances skin penetrati n as well as renders the silicone ils and pr pyl ne glycol miscible is desired. Most preferable is oleyl alcohol, having an HSC f 9.8. A single

phas (i.e. solution) formulation can be prepared from these materials. This vehicle can completely solubilize the sebum levels on the skin wh reas previous minoxidil formulations do not dissolve the amounts of sebum reported to be on the scalp.

For purposes of skin penetration, it is desirable to have less oleyl alcohol in the formulation (e.g., approximately 1:1 ratio of oleyl alcohol to propylene glycol). However, the formulation is not miscible at the 1:1 ratio. A single phase system (at 1:1 oleyl alcohol:propylene glycol) can be prepared by adding some nonvolatile silicone oil (e.g., Dow Corning 200 fluid) and a surfactant (e.g., Union Carbide SILWET L-77).

Further, high concentrations of oleyl alcohol are dermally irritating. Thus, concentrations of oleyl alcohol of from about 10 to about 40% of the total solution are preferred. It is more preferred for cosmetic acceptability to use less than about 20% oleyl alcohol, so that the composition has a less oily "feel".

Preferred proportions of the components are as follows:

Based upon in vitro transdermal data, the concentration of minoxidil should be from about 1.0% to 2.5%; the concentration of propylene glycol from about 12% to 25%; and the concentration of oleyl alcohol from about 6% to 20%. These vehicles give in vitro human skin transport levels of minoxidil that range from about equal to the current 2% minoxidil formulation (20% propylene glycol/60% ethanol/20% water) to approximately 10 fold greater transport, as seen by Example 2.

The use of topical minoxidil compositions is well known to the ordinarily skilled physician or dermatologist. This use is also set forth in U.S. Patents 4,139,619 and 4,596,812, incorporated by reference herein.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is seen more fully by the Examples below.

Example 1

The following formulations are prepared according to the procedure below:

Procedure

(Step 1) Propylen glycol is measured and added to a suitable container. (Step 2) Pr pylen glycol is heated t 52°-58° using a water bath, and heated for 10-15 min nce th temperatur has reached

the required range. (Step 3) Minoxidil is weighed and added slowly to the heated propylene glycol with rapid mixing. Mixing continues until the minoxidil is completely dissolved (approx. 30-40 min). Temperature is maintained at 52°-58°C using the water bath. (Step 4) The minoxidil-propylene glycol solution is cooled to room temperature (approx. 25°C). (Step 5) Oleyl alcohol is measured and added to the cooled step 4 solution and mixed for 1 min. (Step 6) If procetyl-10 is added, it is added to the step 5 mixture and mixed for 1 min at this point. (Step 7) Dow Corning 344 is added to the above mixture and mixed for 5-10 min until a uniform mixture is obtained.

Formulation 1 Minoxidil USP milled (~90 mg/ml propylene glycol to give saturated solution)

| | |
|---|---|
| Propylene Glycol | 15% |
| Oleyl Alcohol USP | 15% |
| Dow Corning 344 (volatile silicone oil) | 70% |

Formulation 2 Minoxidil USP milled (~90 mg/ml propylene glycol)

| | |
|---|---|
| Propylene Glycol USP | 15% |
| Oleyl Alcohol USP | 30% |
| Procetyl-10( PEG 10 cetyl ether) | 10% |
| PGE 10 cetyl ether | |
| Dow Corning 344 | 45% |

Formulation 3 Minoxidil USP milled (~90 mg/ml propylene glycol)

| | |
|---|---|
| Propylene Glycol USP | 12.5% |
| Oleyl Alcohol USP | 25% |
| Procetyl-10 | 10% |
| Dow Corning 344 | 52.5% |

Example 2

Based on the foregoing specification, and on techniques known in the art, all of the compositions of the invention are prepared. Three representative nonaqueous formulations of minoxidil were prepared and are characterized by their dermal characteristics as follows:

| Vehicle | Composition (Vol%) | | | |
|---|---|---|---|---|
| Transport* | Propylene Glycol | Oleyl Alc. | IPA | Vol. Silicone |
| High (~12X) | 25 | 15 | 27 | 33 |
| Medium (~4X) | 15 | 7.5 | 25 | 52.5 |
| Low (~1.5X) | 12 | 6 | 25 | 57 |

* Vehicle transport is defined as the ratio f the peak (1 hr)

transport flux measured for minoxidil through human cadaver skin for the vehicle listed divided by the "standard" reference vehicle (20% propylene glycol/60% ethanol/20% water) peak minoxidil transport measured on a portion of the same piece of skin.

The weight percent of minoxidil in each of these formulations is: 2.3% for the high transport; 1.3% for the medium transport; and 1.1% for the low transport vehicle, while the reference vehicle contains 2.0% minoxidil.

Autoradiographic examination of drug distribution in Macaque monkeys indicates that a formulation containing 20% propylene glycol, 20% oleyl alcohol, 16% isopropanol, and 44% volatile silicone had an approximately sixfold increase in drug delivery into the sebaceous gland in the hair follicle relative to the drug content away from the hair follicle at an equal distance into the skin. The standard formulation had essentially no difference between the amounts in the follicle and outside the follicle. Human in vivo dermal irritation tests show minimal unoccluded dermal irritation for this composition.

Example 3

Using the procedures of the preceding Examples, and techniques known in the art, the following compositions are prepared. (All concentrations are in volume percentages (volume %)).

TABLE 1

Nonaqueous Minoxidil Formulations

| Formulation | Conc. Propylene Glycol | Conc. Oleyl Alcohol | Conc. DC 344 Silicone Oils | Other Composition |
|---|---|---|---|---|
| 1 | 25% | 25% | 50% | 0 |
| 2 | 20% | 30% | 50% | 0 |
| 3 | 20% | 20% | 60% | 0 |
| 4 | 20% | 25% | 55% | 0 |
| 5 | 22.5% | 22.5% | 55% | 0 |
| 6 | 15% | 25% | 60% | 0 |
| 7 | 30% | 20% | 50% | 0 |
| 8 | 25% | 15% | 60% | 0 |
| 9 | 25% | 20% | 55% | 0 |
| 10 | 15% | 30% | 45% | 10% Pro-10* |
| 11 | 12.5% | 25% | 57.5% | 5% Pro-10* |
| 12 | 25% | 10% | 65% | 0 |
| 13 | 15% | 7.5% | 77.5% | 0 |

*Pro-10 = Procetyl-10 (propylene cetyl ether) surfactant added to initial emulsions to impr ve stability.

CLAIMS

1. A topical hair growth composition comprising:

(a) minoxidil;

(b) a solvent, capable of dissolving minoxidil;

(c) a non-polar solvent, which renders the polarity of the total formulation approximately the same as human sebum; and

(d) a cosolvent having a polarity between that of the solvent capable of dissolving the minoxidil and the non-polar solvent, which enhances the delivery of minoxidil through the stratum corneum, said cosolvent in an amount less than that which cause skin irritation.

2. A composition of Claim 1, wherein the solvent capable of dissolving minoxidil is propylene glycol, the cosolvent is a mixture of oleyl alcohol and isopropanol, and the non-polar cosolvent is a volatile silicone oil.

3. A composition of Claim 2, wherein the minoxidil concentration is from about 1.0 to about 2.5% volume %, propylene glycol is from about 12 to about 25% volume %, oleyl alcohol is from about 6 to about 20 volume % w/w, and the isopropanol is from about 16 to about 27 volume %.

4. A composition of Claim 3, selected from the group consisting of formulations having the following proportions:

| Composition | Propylene Glycol | Oleyl Alcohol | Isopropanol | Volatile Silicone |
|---|---|---|---|---|
| (a) | 25 | 15 | 27 | 33 |
| (b) | 15 | 7.5 | 25 | 52.3 |
| (c) | 12 | 6 | 25 | 57 |

5. A composition of Claim 2, selected from the group consisting of formulations having the following proportions:

| Formulation | Conc. Propylene Glycol | Conc. Oleyl Alcohol | Conc. DC 344 Silicone Oils | Other Composition |
|---|---|---|---|---|
| 1 | 25% | 25% | 50% | 0 |
| 2 | 20% | 30% | 50% | 0 |
| 3 | 20% | 20% | 60% | 0 |

| Formulation | Conc. Propylene Glycol | Conc. Oleyl Alcohol | Conc. DC 344 Silicone Oils | Other Composition |
|---|---|---|---|---|
| 4 | 20% | 25% | 55% | 0 |
| 5 | 22.5% | 22.5% | 55% | 0 |
| 6 | 15% | 25% | 60% | 0 |
| 7 | 30% | 20% | 50% | 0 |
| 8 | 25% | 15% | 60% | 0 |
| 9 | 25% | 20% | 55% | 0 |
| 10 | 15% | 30% | 45% | 10% Pro-10* |
| 11 | 12.5% | 25% | 57.5% | 5% Pro-10* |
| 12 | 25% | 10% | 65% | 0 |
| 13 | 15% | 7.5% | 77.5% | 0 |

*Pro-10 = Procetyl-10 (propylene cetyl ether) surfactant added t initial emulsions t impr ve stability.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US 87/02168

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 7/06

## II. FIELDS SEARCHED

Minimum Documentation Searched [7]

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|---|---|
| IPC[4] | A 61 K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

| Category [10] | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No. [13] |
|---|---|---|
| A | WO, A, 85/04577 (G. BAZZANO) 24 October 1985 see page 4, lines 12-35; examples -- | 1-5 |
| A | US, A, 4596812 (CHIDSEY, III et al.) 24 June 1986 see the whole document cited in the application -- | 1-5 |
| A | US, A, 2643375 (V.A. GANT) 23 June 1953 see the whole document | 1-5 |

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* Special categories of cited documents: [10]

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## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
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| 3rd December 1987 | 14 JAN 1988 |
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| EUROPEAN PATENT OFFICE | P.C.G. VAN DER PUTTEN |

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8702168 SA 18604

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 22/12/87
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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO-A- 8504577 | 24-10-85 | EP-A- 0177581 | 16-04-86 |
| US-A- 4596812 | 24-06-86 | US-A- 4139619 | 13-02-79 |
| US-A- 2643375 | | None | |